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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/335,689	06/18/1999	JENNIFER D. TOUSIGNANT	6969.0028	6753

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EXAMINER
SCHNIZER, RICHARD A

ART UNIT	PAPER NUMBER
1635	22

DATE MAILED: 05/22/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/335,689	Applicant(s) TOUSIGNANT ET AL.	
	Examiner Richard Schnizer	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 February 2002* .

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4,6-15,17-26 and 28-46* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4,6-15,17-26 and 28-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

An amendment was received and entered on 2/25/02 as Paper No. 21. Claims 1-4, 6-15, 17-26, and 28-46 are pending and under consideration in this Office Action.

Rejections Withdrawn

After further consideration, the rejection of claims 1-4, 6-15, 31, 32, 35, 36, 39, 40, 43, and 44 under 35 USC 112, second paragraph over the meaning of the term "micellar lipids is withdrawn.

The rejection of claims 1-4, 6-15, 17-26, and 28-30 under 35 USC 112, second paragraph for the lack of a standard allowing one to calculate variation in size distribution is withdrawn in view of Applicant's amendment.

After further consideration, the rejection of claims 1-4, 6-15, 17-26, 28-34 under 35 USC 112, second paragraph for lacking antecedent basis for "the size distribution" is withdrawn.

The rejection of claims 33 and 34 under 35 USC 112, first paragraph for lacking enablement is withdrawn in view of Applicant's amendments.

The rejection of claims 9-11, 13, 14, 17-19, 21, 2, 24-26, 28, 29, and 31-38 under 35 U.S.C. 102 over Harris is withdrawn in view of Applicant's amendments and arguments.

The rejection of claims 9-14, 17-19, 21-26, 28-32, and 35-38 under 35 U.S.C. 102(e) as being anticipated by Unger is withdrawn in view of Applicant's amendments and arguments.

The rejection of claims 1, 9, 14, 15, 17, 19, and 20 under 35 U.S.C. 103(a) as being unpatentable over Harris is withdrawn in view of Applicant's amendments and arguments.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

New Matter

Claims 35-38 stand rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention, for the reasons of record in Paper No. 19.

New claims 35-38 recite the limitation "wherein said method does not necessarily require the formation of a lipid film comprising the cationic lipid." Applicant points to page 16, lines 2-6 to support this limitation. This passage does not refer to, or in any way exclude, the formation of a lipid film. The introduction of claim changes which involve narrowing the claims by introducing elements or limitations which are not supported by the as-filed disclosure is a violation of the written description requirement of 35 U.S.C. 112, first paragraph. See MPEP 2163.05.

Response to Arguments

Applicant's arguments filed 2/25/02 have been fully considered but they are not persuasive.

Applicant argues that the specification at page 15, lines 11-15, and page 16, lines 2-6, combined with Fig. 1(b) provides support for the limitation.

In response, the Office reiterates the point that the text of the specification in no way excludes the formation of a lipid film in the process of the instant invention. Applicant has failed to point to any passage of the specification which clearly supports this limitation. Similarly, while Fig. 1B does not explicitly mention the formation of a lipid film, neither does it explicitly exclude the formation of a lipid film. Even if Fig. 1B did explicitly exclude the formation of a lipid film, it would provide support only for a method in which micellar GL-67 and DMPE-PEG_{5000} are combined without first having formed a lipid film. The Figure provides no support for full claimed scope of combining any cationic lipid with any PEG derivative without the formation of a lipid film. For these reasons the rejection is maintained.

Enablement

Claims 1-4, 6-15, 17-26, and 32 stand rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for micellar complexes and methods of making and using compositions comprising micellar complexes comprising lipid-derivatized PEG, such as are known in the prior art, wherein the size distribution of the all the micellar complexes

within a given composition varies by greater than about 20%, does not reasonably provide enablement for methods of making micellar compositions comprising lipid-derivatized PEG, wherein the size distribution of all the micellar complexes within the composition is less than or equal to about 20%. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims, for the reasons of record.

The claimed inventions encompass methods of making compositions comprising micellar complexes, and methods of using these complexes to deliver biologically active molecules *in vivo*. The complexes comprise at least one cationic lipid, a PEG derivative, and the biologically active substance. The claims require that the size distribution of the micellar complexes cannot vary by more than about 20%. The critical element of the invention is the addition to cationic lipids of a sufficient amount of PEG derivative. Addition of this amount of PEG derivative results in formation of a group of mixed micelles with a narrower size distribution than those observed in at least some prior art formulations. The specification teaches that the amount of PEG derivative which is sufficient varies with "the specific combination of cationic lipid and PEG lipid selected". See page 18, third paragraph. The specification acknowledges that complexes of cationic lipids, biologically active molecules, and lipid-derivatized PEG were known in the prior art. See page 12, lines 4-11. Indeed such compositions are taught by Harris (1998) and Unger (2000). See rejections under 35 USC 102, below. Thus the critical element of

the invention, that which allegedly distinguishes it from the prior art, is the addition of "a sufficient amount of PEG derivative".

Guidance as to what constitutes "a sufficient amount of PEG derivative can be found on pages 18, 19, 25, and 38-42. These passages indicate that "the specific combination of cationic lipid and PEG lipid selected" will affect the amount of PEG derivative which is sufficient to produce the desired micellar complexes, and describe three techniques for determining whether or not one has succeeded in adding a sufficient amount of PEG derivative. The specification discloses a single non-limiting example of what may be a sufficient amount of PEG derivative (see page 37, lines 13-15), but provides no working example which was sufficient to practice the invention. The specification discloses only that the PEG derivative may be added in a certain volume relative to the volume of cationic lipids. See e.g. page 41, first full paragraph. The specification also fails to discuss the principles which govern the effect of PEG derivatives on micelle size, or to otherwise provide any theoretical framework which could be used by one of skill in the art to determine what amount of a PEG derivative, in combination with a cationic lipid, could be used to practice the claimed invention. One might argue that it would not be undue to empirically determine, using the means taught in the specification, the amounts PEG derivative required to practice the claimed invention. However as set forth in *In Re Fisher*, 166 USPQ 18(CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification to persons of ordinary skill in the art; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their

> performance characteristics predicted by resort to **known scientific laws**; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved.

Emphasis added.

In this case, the lack of guidance in the specification concerning what constitutes a sufficient amount of PEG derivative is not complemented by teachings in the prior art. Thus the specification fails to teach the most critical element of the invention. While Applicant is not required to disclose that which is well known in the art, there is an obligation to disclose critical elements of the invention as well as how to use these elements. In Genentech, Inc, v Novo Nordisk A/S, the court found that when the specification omits any specific starting material required to practice an invention, or the conditions under which a process can be carried out, there is a failure to meet the enablement requirement. See 42 USPQ2d 1001.

> It is true, as Genentech argues, that a specification need not disclose what is well known in the art. See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc., 802 F.2d 1367, 1385, 231 USPQ 81, 94 (Fed. Cir. 1986). However, that general, oft-repeated statement is merely a rule of supplementation, not a substitute for a basic enabling disclosure. It means that the omission of minor details does not cause a specification to fail to meet the enablement requirement. However, when there is no disclosure of any specific starting material or of any of the conditions under which a process can be carried out, undue experimentation is required; there is a failure to meet the enablement requirement that cannot be rectified by asserting that all the disclosure related to the process is within the skill of the art. It is the specification, not the knowledge of one skilled in the art, that must supply the novel aspects of an invention in order to constitute adequate enablement. This specification provides only a starting point, a direction for further research.

In this case, the determination of what constitutes a sufficient amount of PEG derivative cannot be considered a minor detail which can be omitted in the process of providing an enabling disclosure.

Because the specification fails to provide critical elements of the invention, one of skill in the art could not practice the invention commensurate in scope with the claims.

Response to Arguments

Applicant's arguments filed 2/25/02 have been fully considered but they are not persuasive.

Applicant argues at pages 7 and 8 of the response that the specification teaches a range of concentrations of PEG derivatives, and examples of preparation of micellar complexes. See page 37, lines 15-18, Figs. 2 and 3, and page 14 of specification. In response the Office reiterates that none of these examples discloses the amount of any lipid or PEG derivative used in any example. The range disclosed at page 37, lines 15-18 is non-limiting, and the Examples in Figs. 2 and 3, and page 14, disclose only the volumes of lipids and PEG-derivative used, not the relative amounts of lipid and PEG derivative. Thus the specification fails to provide any example of the critical limitation which is "a sufficient amount of a PEG derivative". As noted above, the specification also fails to discuss the principles which govern the effect of PEG derivatives on micelle size distribution, or to otherwise provide any theoretical framework which could be used by one of skill in the art to determine what amount of a PEG derivative, in combination with a cationic lipid, could be used to practice the claimed invention. In the absence of any such examples or guidance regarding the single most critical aspect of the invention, one of skill in the art is left to combine lipids and PEG derivatives and assay the resulting complexes until arriving

at the conditions which result in meeting the claimed size distribution limitations. Applicant argues that such experimentation is not undue, but this argument lacks support, and is in direct contradiction of the findings of the court in *In re Fisher* and Genentech, Inc, v Novo Nordisk A/S. See above. Applicant is correct in stating that *In re Fisher* is concerned with the relationship between the degree of disclosure in the application and the scope of enablement. However, in this case, the specification fails to disclose what is "a sufficient amount of a PEG derivative" for any combination of PEG derivatives and lipids, except in terms of the nature of the resulting complex. *Fisher* clearly states that "in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with the degree of unpredictability of the factors involved." In this case, the prior art provides no basis for predicting the effect of the concentration of PEG derivatives on the size distribution of micellar complexes, thus the specification must teach what is missing from the prior art. Because the specification fails to do so, there is a failure to meet the enablement requirement.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 31-34, 41 and 42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 31-34 are indefinite because it is unclear what are the metes and bounds of "traditional lipid complexes". At page 5 of the response, Applicant asserts that "traditional lipid complexes" is defined at page 15, lines 11-17. This is incorrect, page 15, lines 11-17 deals with the term traditional cationic amphiphile complexes. Further, this section does not deal with the size distribution of complexes, but rather with size variation. Support for the size distribution of "traditional lipid complexes" may be found at page 17, lines 10-13. However, the specification does not define this term in a limiting manner, so it is unclear which lipid complexes in the prior art can be considered to be traditional, and which cannot. For this reason the metes and bounds of the claim are unclear.

Claims 41 and 42 are indefinite because it is unclear what is intended by the limitation "preferably". It is unclear how "preferably" is intended to affect the metes and bounds of the invention. It is unclear whether or not the claimed material is required to bind airway epithelial cells. See MPEP 2173.05 (d) which reads:

> 2173.05(d) Exemplary Claim Language ("for example," "such as")
> Description of examples or preferences is properly set forth in the specification rather than the claims. If stated in the claims, examples and preferences lead to confusion over the intended scope of a claim. In those instances where it is not clear whether the claimed narrower range is a limitation, a rejection under 35 U.S.C. 112, second paragraph should be made.

Response to Arguments

Applicant's arguments filed 2/25/02 have been fully considered but they are not persuasive.

Applicant argues at page 13 of the response that the term "preferably" is definite within the context of the claim. This argument is unpersuasive because it lacks support.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 39-42 stand rejected under 35 U.S.C. 102(b) as being anticipated by Harris et al (US Patent 5,719,131, issued 2/17/98) for the reasons of record in Paper Nos. 8, 10, and 19..

Harris teaches methods of making micellar compounds comprising a cationic lipid, a PEG derivatized colipid, and DNA. See column 26, lines 4-11 and 32-36; column 37, lines 24-53; and column 45, line 56 to column 46, line 5. Harris teaches the delivery of DNA to human airway epithelial cells. See Examples 2 and 3, columns 39-42.

Thus Harris anticipates the claims.

Claims 33, 34, 39-46 are rejected under 35 U.S.C. 102(e) as being anticipated by Unger (US Patent 6,028,066, filed 5/2/97) for the reasons of record in Paper Nos. 8, 10, and 19.

Unger teaches a method of making micellar complexes by combining micellar lipids with a bioactive agent which may be DNA. See column 79, lines 20-37; column 2, lines 59-65; column 6, lines 10-24, especially lines 22 and 23; and column 6, lines 55-57. The micellar lipids may comprise PEG-modified lipids. See column 22, line 19 to column 24, line 1, especially column 22, lines 60-67. Unger also teaches delivery of the complexes to mammalian airway cells. See column 84, lines 24-28. The complexes may be less than from 5 nm to 2 microns in size, alternatively they may be between 5 nm and 200 nm. See column 30, lines 44-48. Thus Unger teaches at least one composition that has a size distribution which is narrower than that of a traditional lipid complex. That is the size distribution of a group of complexes from 5-200 nm must be narrower than that of a group of complexes of 5-2000 nm.

Thus Unger anticipates the claims.

Response to Arguments

Applicant's arguments filed 2/25/02 have been fully considered but they are not persuasive.

Applicant argues at pages 13 and 14 of the response that the rejections of claims 39-42 over Harris and claims 33, 34, and 39-42 over Unger are moot in view of Applicant's amendments. This is unpersuasive because it lacks support.

With respect to the rejection of claims 43-46 over Unger, Applicant asserts that the Office has presented no absolutely no arguments in support of the rejection. Applicant's attention is

directed to page 12 of Paper No. 19, the pertinent portions of which are reproduced in the rejection immediately above. The rejection clearly shows where Unger teaches each limitation of the claims. For this reason, the rejection is maintained.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner(s) should be directed to Richard Schnizer, whose telephone number is 703-306-5441.

The examiner can normally be reached Monday through Friday between the hours of 6:20 AM and 3:50 PM. The examiner is off on alternate Fridays, but is sometimes in the office anyway.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John Leguyader, can be reached at 703-308-0447. The FAX numbers for art unit 1632 are 703-308-4242, and 703-305-3014. Additionally correspondence can be transmitted to the following RIGHTFAX numbers: 703-872-9306 for correspondence before final rejection, and 703-872-9307 for correspondence after final rejection.

Inquiries of a general nature or relating to the status of the application should be directed to the Patent Analyst Trina Turner whose telephone number is 703-305-3413.

Richard Schnizer, Ph.D.

JAMES KETTER
PRIMARY EXAMINER